Uncertainties: which intervention reduces the risk of preterm birth in women with risk factors?

Uncertainties: Which intervention reduces the risk of preterm birth in women with risk factors?

Journal:	*BMJ*
Manuscript ID	BMJ.2016.034695.R2
Article Type:	Practice
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
Complete List of Authors:	Stock, Sarah; University of Edinburgh MRC Centre for Reproductive Health, Obstetrics and Gynaecology Ismail, Khaled; University of Birmingham, College of Medical and Dental Sciences
Keywords:	Preterm Birth, Cervical Cerclage, Progesterone, Cervical Pessary, Cervical Length, Multiple Pregnancy, Suture Material

Uncertainties: Which intervention reduces the risk of preterm birth in women with risk factors?

Sarah J Stock[1], Khaled M K Ismail[2*]

[1]Senior Clinical Lecturer and Subspecialist Maternal and Fetal Medicine

Tommy's Centre for Maternal and Fetal Health

MRC Centre for Reproductive Health

University of Edinburgh Queen's Medical Research Institute

Little France

Edinburgh

EH16 4TJ

[2]Professor of Obstetrics and Gynaecology

The Birmingham Centre for Women's and Children's Health

College of Medical and Dental Sciences

University of Birmingham

Edgbaston

Birmingham

B15 2TT

E-mail: k.ismail@bham.ac.uk

* Corresponding author

Search terms: Preterm Birth, Cervical Cerclage, Progesterone, Cervical Pessary, Cervical Length, Multiple pregnancy, Suture material.

Word Count: 1,427 (including online material)

Introduction

The aim of preventing preterm birth is to improve the health of babies by prolonging pregnancy. Preterm birth (PTB), or delivery before 37 weeks gestation, affects 7.3 % of pregnancies in the UK [1]. Around 75% result from spontaneous preterm labour. The remaining 25% are induced for medical reasons are not considered further in this article.

Who is at risk?

Specific obstetric clinical risk factors and / or ultrasound scan findings associated with an increased risk of spontaneous PTB are listed in box 1. However these have poor predictive value. Women with multiple pregnancy are also at high risk of preterm birth, and their management is discussed in supplementary online material.

Box 1: Risk factors for PTB [4 5]

Clinical History*:

- *History of mid-trimester loss
- *History of preterm prelabour rupture of membranes in a previous pregnancy
- *History of PTB in a previous pregnancy
- *History of cervical treatment for CIN

The presence of any of these clinical risk factors can be considered a trigger for cervical length screening by transvaginal ultrasound scan.

Imaging:

- Short cervix (less than 25mm) on transvaginal ultrasound examination

Appraising the evidence

Three therapeutic interventions are available for women at risk of spontaneous PTB (Table 1). However, considerable uncertainty exists over the effectiveness of these interventions, in part because clinical trials are hard to perform. Large numbers of trial participants are needed because the majority of high-risk women will deliver at term, even without treatment. It is both difficult and expensive to include neonatal and childhood outcomes in trials, therefore trials mainly focus on rates of preterm birth, not longer-term health outcomes of babies. Furthermore, inconsistencies in definitions, inclusion criteria and outcomes in studies mean it is difficult to summarise trial data in meta-analyses, and difficult to interpret relevance of the findings to individual women in the clinic setting.

What is the evidence of uncertainty?

See Table 2 for summary of evidence.

Singleton Pregnancies

Cervical Cerclage

An individual patient data (IPD) meta-analysis (5 RCTs involving 504 women) and a systematic review (12 RCTs involving 3328 women) showed that cervical cerclage delayed the gestational age at delivery and reduces PTB in women at risk of early delivery [7 8]. There was no statistically significant difference in perinatal mortality with cerclage,[7 8]. The IPD meta-analysis, which only included women with a short cervix (25mm), showed a reduction in composite neonatal morbidity in the cerclage group [7]. However, no reduction in morbidity was seen in the larger meta-analysis of summary

data, where partcipants in the included studies had a more diverse range of risk factors for PTB [8]. For women, higher rates of vaginal discharge, vaginal bleeding, pyrexia, and caesarean section were found in those who underwent cerclage [8].

Vaginal Progesterone

An IPD meta-analysis (5 RCTs involving 775 women and 827 infants) and a systematic review (36 RCTs involving 8523 women and 12,515 infants) support vaginal progesterone use to reduce PTB in women with singleton pregnancies at risk of PTB [9 10]. The results of both systematic reviews are mainly driven by one RCT in which all pregnant women were screened for cervical length with transvaginal ultrasound and progesterone given if the cervix was 10-20mm [11]. It is difficult to interpret these data where universal screening of cervical length in pregnancy is lacking, such as in the UK [12].

A large UK based RCT (OPPTIMUM) was published after these systematic reviews and the release of NICE guidelines [13]. OPPTIMUM is the largest RCT of vaginal progesterone and the only one powered to include a childhood primary outcome. It included women at risk of PTB (Box 1) and found that vaginal progesterone did not reduce any of the primary outcomes: PTB, neonatal death or severe morbidity, or the childhood neurodevelopment development (standardised cognitive score (Bayley-III)) at 2 years of age [13]. There were no harms associated with progesterone use [13].

Cervical Pessary

Two randomised trials of several hundred women have evaluated the Arabin pessary with a short cervix on transvaginal ultrasound [14 15]. The smaller trial reported a

benefit in using the pessary [14], whilst the larger trial found no statistically significant difference in PTB rate between women randomised to cervical pessary and those randomized to expectant management [15].

Comparison of treatments to prevent PTB

As yet there are no reported trials comparing the effectiveness of cervical cerclage, progesterone supplementation and cervical pessary against each other when used in isolation or in combined management strategies in women at risk of PTB.

Multiple Pregnancies

Overall there is less evidence regarding management in multiple pregnancies. See Table 3 (online) for summary of evidence.

Cervical cerclage

A systematic review found no evidence that cervical cerclage reduces PTB in women with multiple pregnancy [16]. However, only 128 women with multiple pregnancy were included, firm conclusions about benefits and harms cannot be made.

Vaginal progesterone

Evidence from an IPD meta-analysis of 1,7345 women with multiple pregnancies shows no benefit from vaginal progesterone in this group as a whole [17]. However, progesterone did reduce poor perinatal outcome in a small subgroup of 116 women who had both multiple pregnancy and a short cervix. Further evidence is required to confirm this observation [17].

Cervical pessary

Two randomised controlled trials included twin pregnancies with no other risk factors for preterm birth and found there was no difference between cervical pessary compared to routine care [18 19]. A third randomised controlled trial, confined to women with multiple pregnancy and a short cervix has recently been published, and did show a reduction in PTB with a cervical pessary [20].

Is ongoing research likely to provide relevant evidence?

Clinical trials addressing uncertainties in clinical management of women at risk of spontaneous PTB were identified through a search of clinical trials databases (Box 2) and are summarized in table 4. Only two of the five identified studies (C-STITCH and STOPPIT-2) have primary outcomes focused on mortality or neonatal health, with other studies using the surrogate outcome of gestation at delivery.

An individual patient data meta-analysis of vaginal progesterone to prevent preterm birth is planned by the US Patient Centred Outcomes Research Initiative (http://www.pcori.org), which should help clarify whether progesterone is effective, and if so, which women should be offered it.

It is essential that future studies use standard definitions, protocols and core outcomes so that data regarding important, but uncommon outcomes (like neonatal mortality) can be readily synthesized and guide decision-making.

Box 2: Search Strategy

We searched clinical trials databases (www.controlled-trials.com/isrctn/; http://clinicaltrials.gov/) and the UKCRN Portfolio database (http://public.ukcrn.org.uk/search/) with search terms relating to PTB, miscarriage, perinatal mortality and neonatal morbidity. We also had personal communication with the Royal College of Obstetricians and Gynaecologists Preterm Birth Clinical Study Group.

What should we do in the light of the uncertainty?

Parents should be aware that a reduction in incidence of early delivery may not necessarily translate into improved health in children.

It is reasonable to follow NICE (UK) guidance on the prevention of preterm birth and offer cervical cerclage when there has been a previous PTB, midtrimester loss, preterm prelabour rupture of membranes or cervical treatment, and the cervix is short [6]. Alternatively, progesterone may be offered [6], however, the OPPTIMUM trial, (published after the NICE guideline), showed no benefit of vaginal progesterone in this group [13]. We were unable to find any international guidance relating to prevention of preterm birth.

We believe that further evidence is needed before offering the cervical pessary out of a research setting [14 15].

In our opinion women with multiple pregnancies should not be offered treatments to prevent PTB (except in the context of clinical trials) as no clear benefit has been

shown [16-20].

We suggest that clinicians share the uncertainly about PTB and offer women the opportunity to participate in relevant clinical trials.

What you need to know

- The best intervention for prevention of spontaneous PTB in women with risk factors is still unclear In women with a singleton pregnancy risk of PTB and a short cervix the evidence for use of cervical cerclage is clearer than that for progesterone or cervical pessary.
- Discuss with parents that prevention of pre term delivery may not necessarily translate into improved health in children.

BOX 3 Recommendations for future research

Future research should:

- Use standard definitions, protocols and core outcomes so that data can be meta-analysed.
- Be adequately powered for important outcomes including neonatal morbidity and periatal mortality, rather than surrogate outcomes such as PTB.
- Include consent to allow follow-up studies so that long term outcomes can be determined.
- Data from trials should be made available for subsequent meta-analysis

How patients were involved in the creation of this article

"Which interventions are most effective to predict or prevent PTB?" was the number one uncertainty prioritised by the James Lind Alliance PTB Priority Setting Partnership, which brings together patients, carers and clinicians in partnership to identify and prioritise research questions and uncertainties relating to a healthcare problem. [20]. No patients were directly involved in creating this article.

References

1. Gestation-specific Infant Mortality in England and Wales 2014. http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/datasets/gestationspecificinfantmortalityinenglandandwalesreferencetables. Accessed 26th July 2016.

2. Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev 2013(10):CD001055.

3. Sandall J, Soltani H, Gates S, et al. Midwife-led continuity models versus other models of care for childbearing women. Cochrane Database Syst Rev 2016;4:CD004667.

4. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. Obstet Gynecol 2007;110(2 Pt 1):405-15.

5. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet 2008;371(9606):75-84.

6. Preterm Labour and Birth: NICE guideline (NG25), 2015.

7. Berghella V, Rafael TJ, Szychowski JM, et al. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. Obstet Gynecol 2011;117(3):663-71.

8. Alfirevic Z, Stampalija T, Roberts D, et al. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. The Cochrane database of systematic reviews 2012;4:CD008991.

9. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol 2012;206(2):124 e1-19.

10. Dodd JM, Jones L, Flenady V, et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. The Cochrane database of systematic reviews 2013;7:CD004947.

11. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2011;38(1):18-31.

12. Bazian. Screening for Preterm Labour in asymptomatic, low-risk women. External review against programme appraisal criteria for the UK National Screening Committee (UK NSC): UK National Screening Committee, 2014.

13. Norman JE, Marlow N, Messow CM, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016.

14. Goya M, Pratcorona L, Merced C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. Lancet 2012;379(9828):1800-6.

15. Nicolaides KH, Syngelaki A, Poon LC, et al. A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth. N Engl J Med 2016;374(11):1044-52.

16. Rafael TJ, Berghella V, Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. The Cochrane database of systematic reviews 2014;9:CD009166.

17. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG : an International Journal of Obstetrics and Gynaecology 2014; 122(1):27-37.

18. Liem S, Schuit E, Hegeman M, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. Lancet 2013;382(9901):1341-9.

19. Nicolaides KH, Syngelaki A, Poon LC, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. Am J Obstet Gynecol 2016;214(1):3 e1-9.

20. Goya M, de la Calle M, Pratcorona L, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). Am J Obstet Gynecol 2016;214(2):145-52.

21. Crowe S US, Duley L, Oliver S. . Description of a workshop to set research priorities in preterm birth. James Lind Alliance 2014.

Contributors

SJS and KMKI planned the organization, content, and structure of the article. SJS performed the literature search and drafted the article, with crucial edits and additions from KMKI. Both authors participated in subsequent revisions. KMKI is guarantor.

Disclosure Statement

We have read and understood the BMJ policy on declaration of interests and declare the following interests: SJS is an unpaid representative on Scottish Governmental Advisory Groups, and a member of the RCOG Preterm Birth Clinical Study Group and has received travel expenses to attend meetings relating to these roles. SJS is chief investigator and a co-investigator in trials relating to preterm birth funded by NIHR HTA, and the institution she works at has also received research funding from Sparks, Tommy's and the British Maternal and Fetal Medicine (BMFMS) Society. SJS has been provided with ultrasound equipment and software for use in studies of preterm birth research from GE and Philips. SJS has received Honoraria for contributing to book chapters, and travel and accommodation expenses as an invited speaker at conferences and academic institutions. KMKI is chief investigator for C-STICH, funded by NIHR HTA. KMKI receives travel and accommodation expenses as an invited speaker at conferences and academic institutions; however, honoraria or royalty fees generated from academic activities funds academic activities related to women's health. The authors had no support from any organization for the submitted work. The authors grant the publishers a worldwide license.

Acknowledgments

The authors would like to thank members of the RCOG Preterm birth Clinical Study Group for advice on future research recommendations and information on ongoing trials.

Licence for Publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government

Tables

Table 1

Treatment	What is it?	Usual Timing	Evidence and Guidance for use
Cervical Cerclage	A purse string suture that strengthens and tightens the cervix. Usually inserted under regional (spinal) or general anaesthesia.	Inserted between 12 and 24 weeks gestation, and removed at 37 weeks gestation or if there are signs of labour before this.	Current NICE guideline recommends offering cerclage to women with a clinical risk factor (Box 1) and a short cervix on ultrasound (<25mm) but mainly low or moderate quality evidence.
Progesterone supplements	Intravaginal progesterone is the only formulation available in the UK. Usually prescribed as once daily pessaries.	Commenced between 16 and 22 weeks gestation, and continued to 34-36 weeks gestation.	Current NICE guideline recommends offering vaginal progesterone to women with a clinical risk factor (Box 1) and/or a short cervix on ultrasound (<25mm) but mainly low or moderate quality evidence.
Cervical Pessary (Arabin)	A silicon ring that sits over the cervix and works by supporting the cervix and tilting it posteriorly. No anaesthesia or analgesia is required for insertion. There is only one cervical pessary on the market – Arabin.	Inserted between 18 and 22 weeks gestation, and removed at 37 weeks gestation or if there are signs of labour before this.	Not reviewed in current NICE guideline.

Table 1: Treatment options for preterm birth

Comment [SS1]: Images for each sent in separate file of supplementary material

Table 2

	Study design	Population	Intervention/ Comparator	Reduction in PTB?	Reduction in Perinatal Mortality?	Reduction in Adverse Neonatal Outcome?
Cervical Cerclage	Systematic review and IPD level meta-analysis (5 trials; 504 women/infants) [7]	Cervical length less than 25mm	Cervical Cerclage/Expectant Management	**Yes** <35 weeks 28.4% vs 41.3% RR 0.70 95% CI 0.55–0.89 (5 trials; n=504)	**No** 8.8% vs 13.8% RR 0.65 95% CI 0.40–1.07 (5 trials; n=504)	**Yes** 12.8% vs 20.1% RR 0.64 95% CI 0.43-0.96 (5 trials; n=504)
	Systematic review and meta-analysis of summary statistics (8 trials; 2392 women, 2391 infants) [8]	High risk of preterm birth (history and/or short cervix)	Cervical Cerclage/Expectant Management	**Yes** <34 weeks 17.6% vs 23.1% RR 0.79 95% CI 0.68-0.93 (8 trials; n=2392)	**No** 8.4% vs 10.7% RR 0.78 95% CI 0.61-1.00 (8 trials; n=2391)	**No** 17.5% vs 23.2% RR 0.82 95% CI 0.61, 1.09 (4 trials; n=817)
Vaginal Progesterone	Systematic review and IPD level meta-analysis (5 trials; 775 women, 827 infants) [9] **	Cervical length of ≤25mm	Vaginal Progesterone/ Placebo	**Yes** <34weeks 16.0% vs 27.1% RR 0.61 95% CI 0.47–0.81 (5 trials; n= 775)	**No** 3.4% vs 5.3% RR 0.63 95% CI 0.34-1.18 (5 trials; n= 827)	**Yes** 9.7% vs 17.3% RR, 0.57 95% CI, 0.40-0.81 (5 trials; n= 827)
	Systematic review and meta-analysis of summary statistics (5 trials; 1165 women/infants) [10]	Previous preterm delivery	Vaginal Progesterone*/Placebo or no treatment	**Yes** <34 weeks 3.5% vs 21.7% RR 0.21	**No** 3.7% vs 5.6% RR 0.67 95% CI 0.34- 1.29	-

				95% CI 0.10-0.44 (4 trials; n=454)	(2 trials; n=752)	
	Systematic review and meta-analysis of summary statistics (2 trials; 732 women/infants) [10]	Ultrasound identified short cervix	Vaginal Progesterone*/ Placebo	**Yes** <34 weeks 20.8% vs 36% RR 0.58 95% CI 0.38-0.87 (1 trial ; n=250)	**No** 3.0% vs5.3% RR 0.56 95% CI 0.27-1.17 (2 trials; n=732))	-
	Randomised Control Trial (1228 women/infants) [13]	High risk of PTB (history &/or short cervix or positive fetal fibronectin + clinical risk factor)	Vaginal Progesterone/ Placebo	**No** <34 weeks 18% vs 16% Adjusted OR 0·86 95% CI 0·61-1·22	**No** 1% vs 1% Unadjusted OR 1.14 95% CI 0.41-3.17	**No** Adjusted OR 0·62 10% vs 7% 95% CI 0·38-1·03
Cervical Pessary	Randomised Trial (1 trial; 385 women/infants) [14]	High risk of preterm birth (history and/or short cervix)	Cervical Pessary/ Expectant Management	**Yes** <34 weeks 6.3% vs 26.8% RR 0.24 95% CI 0.13-0.43 (1 trial; n=385)	**No** 0 vs 0.5% RR 0.0 95% CI [0.0-0.0] (1 trial; n=385)	-
	Randomised Trial (932 women/infants) [15]	Ultrasound identified short cervix (<25mm)	Cervical Pessary/ Expectant Management (Progesterone was given if cervical length <15mm in either group)	**No** <34 weeks 12.0% vs 10.8%, OR 1.12 95% CI 0.75 –1.69	**No** 3.2% vs 2.4% OR 1.38 95% CI 0.63-3.4	**No** 6.7% vs 5.7%, OR 1.18 95% CI 0.69-2.03

Summary data of Systematic Reviews of Randomised Trials of Interventions to Prevent Preterm Birth (PTB) in Women with Risk Factors and Singleton Pregnancy.

We performed searches in Medline and the Cochrane Libraries using search terms for PTB combined with terms for progesterone, cervical pessary, Arabin and cervical cerclage and a filter for systematic reviews of randomized control trials restricted to studies in humans.

*This review included data from trials of intramuscular 17 alpha hydroxyprogesterone acetate, which is not available in the UK. Data presented here are restricted to those relating to vaginal progesterone.

** review included some multiple pregnancies

IPD : Individual patient level data meta-analsysis

RR: Risk Ratio

OR: Odds Ratio

CI: Confidence Interval

Yes and No indicate statistically significant difference in outcome

Table 3 (online only)

	Study design	Population	Intervention/ Comparator	Reduction in PTB?	Reduction in Perinatal Mortality?	Reduction in Adverse Neonatal Outcome?
Cervical Cerclage	Systematic review and meta-analysis of summary statistics (5 trials, 128 women, 262 infants) [16]	Multiple pregnancy	Cervical Cerclage vs Expectant Management	**No** 46.2% vs 31.8% RR 1.16 95% CI 0.44-3.06 (4 trials: n = 83)	**No** 19.2% vs 9.5%; RR 1.74 95% CI 0.92-3.28 (5 trials, n =262)	**No** 40.4% vs 20.3% RR 1.54 95% CI 0.58 -4.11, (3 trials; n = 116)
Vaginal Progesterone	Systematic review and IPD level meta-analysis (7 trials; 1,735 women, 3470 infants) [17]	Multiple pregnancy	Vaginal Progesterone*/ Expectant Management	**Yes** <35 weeks 26% vs 28% RR 0.94 95% CI 0.8-1.1 (7 trials; n=1,735)	**No** 2% vs 2% RR 0.97 95% CI 0.65-1.4 (7 trials; n=3470)	**No** 13% vs 13% RR 0.97 RR 0.96 95% CI 0.83–1.1 (7 trials; n=3470) ----------** Short cervix subgroup 26.8% vs 63.5%; RR 0.57 95% CI 0.47-0.70 (n=116)
Cervical Pessary	Randomised Trial (808 women; 1634 infants) [18]	Multiple pregnancy	Cervical Pessary vs Expectant Management		**No** 4% vs 4% RR 0.83 95% CU 0.41-1.68 [1 trial; n=1,634]	**No** 13% vs 14% RR 0·98, 95% CI 0·69–1·39 [1 trial; n=1,634] Short cervix subgroup 12% vs 29%

						RR 0.40 95% CI 0.19-0.83 (n=133)
	Randomised Trial (1,180 women; 2,354 infants)[19]	Twins	Cervical Pessary vs Expectant Management	**No** <34 weeks 13.6% vs. 12.9% RR 1.05 95% CI 0.79-1.41	**No** 2.5% vs. 2.7% RR 0.91 95% CI 0.55-1.49	**No** 10.0 vs. 9.2% RR 1.09 95% CI 0.85-1.41 Short cervix subgroup 17.1% vs 14.7% RR 1.20 95% CI 0.77-1.89 (n=396)
	Randomised Trial (137 women; 274 infants) [20]	Twins and short cervix (≤25mm)	Cervical Pessary vs Expectant Management	**Yes** <34 weeks 16.2% vs 39.4% RR 0.41 95% CI 0.22-0.76	**No** No deaths in either group	**No** 5.9% vs 9.1% RR 0.64 95% CI 0.27-1.50

Table 3: Summary data of Systematic Reviews of Randomised Trials of Interventions to Prevent Preterm Birth (PTB) in Women with Risk Factors and Multiple Pregnancy.

We performed searches in Medline and the Cochrane Libraries using search terms for PTB combined with terms for progesterone, cervical pessary, Arabin and cervical cerclage and a filter for systematic reviews of randomized control trials restricted to studies in humans.

*This review included data from trials of intramuscular 17 alpha hydroxyprogesterone acetate, which is not available in the UK. Data presented here are restricted to those relating to vaginal progesterone.

IPD : Individual patient level data meta-analsysis

RR: Risk Ratio

OR: Odds Ratio

CI: Confidence Interval

Yes and No indicate statistically significant difference in outcome

Table 4: Ongoing relevant trials

Title Setting [Trial Registration or ID] Funder	Population	Intervention	Comparator(s)	Primary Outcome	Comments
C-STITCH: Cerclage suture Type for an Insufficient Cervix and its effect on Health outcomes) UK Multicentre [ISRCTN15373349] NIHR HTA	Women with singleton pregnancy and indication for cervical cerclage (n=900).	Cervical cerclage using monofilament (nylon) suture	Cervical cerclage using multifilament (Mersilene tape) suture	Pregnancy loss rate (miscarriage and perinatal mortality, defined as any still birth or neonatal death in the first week of life)	Primary outcome influenced by patient and public involvement group, and chosen as most relevant to pregnant women.
MAVRIC: A multicentre randomised controlled trial of transabdominal versus transvaginal cervical cerclage UK Multicentre [ISCTRN33404560] The Moulton Charitable Foundation	Women with singleton pregnancy and previous failed vaginal cerclage (n=133)	Abdominal Cerclage	High or Low Vaginal Cerclage	Spontaneous PTB < 32 weeks	Recruitment closed and reports in preparation
STOPPIT-2: An open randomised trial of the Arabin pessary to prevent preterm birth in twin pregnancy, with health economics and acceptability UK Multicentre [ISCTRN02235181] NIHR HTA	Women with multiple pregnancy and a short cervix	Cervical (Arabin) Pessary	Standard care	**Obstetric:** Spontaneous PTB <34 weeks. **Neonatal:** Composite morbidity and mortality	Includes a neonatal primary outcome.
SuPPoRT: Stitch, Progesterone or Pessary: a Randomised Trial UK Multicentre [EudraCT 2015-000456-15] NIHR Research Fellowship	Women with singleton pregnancy at high risk of spontaneous preterm birth with a short cervix (<25mm) (n=540)	Cervical Cerclage	Vaginal Progesterone 200mg or Cervical Pessary	Delivery <37 weeks	2 trials comparing interventions in women with risk factors for PTB.
ReCAP: Randomised Trial into Prevention of Preterm Birth: Feasibility Study UK 2 Centres [UKCRN ID 18675]	Women with singleton pregnancies at high risk of spontaneous preterm birth with a short cervix	Cervical Cerclage	Vaginal Progesterone 200mg or Cervical		

NIHR RfPB	(<3rd centile) (Feasibility – no specified sample size)		Pessary		

Abbreviations: HTA: Health Technology Assessment, RfPB: Research for Patient Benefit, PTB: Preterm Birth